IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: TAKAHASHI=38

In re Patent Application of:	Conf. No.: 7118
Masami TAKAHASHI et al	Examiner: Nizal S,
U.S. Appln No.: 10/581,045	Chandrakumar
Filed: May 30, 2006	Art Unit: 1625

For PIPERIDINE COMPOUND AND PROCESS
: FOR PREPARING THE SAME

Honorable Commissioner for Patents
U.S. Patents and Trademark Office
Customer Service Window
Randolph Building, Mail Stop Amendment
401 Dulany Street
Alexandria, VA 22313

DECLARATION UNDER 37 CFR 1.132

SIR:

I. I, Shuichi Towa, a citizen of Japan, having an address of LM Musashiurawa Garden 602, 7-21-31, Shikatebukuro, Minami-ku, Saitama-shi, Japan, declares and states as follows.

I am one of the research project members of the subject matter of the above-identified application.

I graduated from the Faculty of Science, Osaka City University, Japan, in March, 1989, and completed the post graduate course in March, 1991.

I am a member of the Japanese Society of Toxicology.

Since April, 1992, I have been an employee of Tanabe Seiyaku Co., Ltd., 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka,

Japan. I had been in charge of toxicology at the Toxicology and DMPK Research Laboratories of the company from April, 1992 to September, 2007. I am presently a member of Safety Research Laboratory, at the Research Division of Mitsubishi Tanabe Pharma Corporation (Mitsubishi Tanabe Pharma Corporation was created through the merger of Tanabe Seiyaku Co., Ltd. and Mitsubishi Pharma Corporation on October 2007.).

In order to show more clearly that the present invention is patentable over Alvaro et al. (WO 03/066589 A1), I have conducted comparative experiments as mentioned below under my supervision.

II. Comparative experiments

An object of the experiment is to show evidences that it would not have been obvious to someone of ordinary skill in the art of medicinal chemistry to expect the compounds of the present invention from the compounds disclosed in Alvaro et al., since the excellent effects of the present invention could never be expected from Alvaro et al.

Experimental Example (Phospholipidosis)

According to a method recited in Experimental and toxicologic pathology, vol. 58, pp. 375-382, 2007, CHL/IU cells were seeded in 96-well micro plates and incubated in MEM culture medium containing 10% fetal bovine serum for 24 hours. To the above-mentioned culture medium containing a fluorescent-labeled phospholipid analogue, N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt (NBD-PE) were added test compounds dissolved in dimethylsulfoxide so that the

final concentration of the test compounds is 6.25 to 100 μM and the final concentration of the dimethylsulfoxide is 1%. The test compounds were the compounds of the present invention and the compounds of Alvaro et al. [WO 03/066589 A1] as shown in the following table. After 24 hours of culture, fluorescence of the each well was measured. The phospholipidosis-inducing potential of the test compounds was evaluated based on the fluorescence intensity. Cells exposed by 1.56 to 25.0 μM amiodarone were used as positive control. Cells to which no test compounds are added were used as negative control. In the concentration range in which 50% or more of the cell survival rate after addition of the test compounds is secured, an well exhibiting 1/4 or more of the maximum fluorescence intensity at the time of amiodarone exposure was judged as phospholipidosis-inducing potential positive (+), and an well exhibiting less than 1/4 of the same was judged as phospholipidosis-inducing potential negative (-). The results are shown in the following table.

Example No. of the compounds of the present invention	Pospholipidosis-inducing potential	Known compounds of Alvaro et al.	Pospholipidosis-inducing potential
5(4)	-	Known compound 1	+
9	-	Known compound 2	+
13	-	Known compound 3	+
14	-	Known compound 4	+
15	-	Known compound 5	+
16	-		
17	-		

The compounds (Known compounds 1 to 5) of Alvaro et al. shown in the right column of the above-table are as follows.

Known compound 1: 4-(R)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (Example 5a of Alvaro et al.).

Known compound 2: 4-(S)-Dimethylamino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (Example 4b of Alvaro et al.).

Known compound 3: 4-(S)-(2-Fluoroethyl)-amino-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (Example 6b of Alvaro et al.).

Known compound 4: 4-(S)-(2-Fluoro-ethylamino)-2-(R)-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride (Example 7b of Alvaro et al.).

Known compound 5: 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-morpholino-piperidine-1-carboxylic acid 1-[(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (Example 27 of Alvaro et al.).

As can be seen from the above table, the compounds of the present invention have no pospholipidosis-inducing potential as contrasted to the compounds of Alvaro et al. Accordingly, it would be clear that the compounds of the present invention have a small likelihood of leading to a toxicity development and have high safety as compared to the compounds of Alvaro et al. This property of the compounds of the present invention is

an extremely beneficial effect when developing the compounds as a medicine.

III. Conclusion

I believe that the above results would indeed be surprising and could never be expected from the disclosure of Alvaro et al. Thus, I do not believe that the present invention is unpatentable over Alvaro et al.

IV. I further declare that all statements made herein of may own knowledge are true and that all statements made in information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: December 10, 2007 Shuichi Towa

Shuichi Towa

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VERIFICATION OF TRANSLATION

SIR:

The undersigned, Yuriko Sumino, hereby declares the following:

That I am knowledgeable in the Japanese and English languages.

That I have reviewed page 16, lines 14-15 of the Japanese language text of PCT/JP2004/017543 which corresponds to page 20, lines 15-18 of the English language specification, and

That I verify that the attached document is an accurate translation thereof.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. Further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

December 11, 2007
Date

Yuriko Sumino
Yuriko SUMINO

[0036] 本発明の化合物[I]またはその薬理的に許容しうる塩は、優れたタキキニン受容体拮抗作用、特にSP受容体拮抗作用を有し、哺乳動物(例えば、マウス、モルモット、スナネズミ、フェレット、ラット、ハムスター、ウサギ、ネコ、イヌ、ウシ、ヒツジ、サル、ヒトなど)に対する、炎症もしくはアレルギー性疾患(例えば、アトピー、皮膚炎、ヘルペス、乾癬、喘息、気管支炎、喀痰、鼻炎、リューマチ関節炎、変形性関節炎、骨粗鬆症、多発性硬化症、結膜炎、眼炎、膀胱炎など)、疼痛、偏頭痛、神経痛、掻痒、咳、さらに中枢神経系の疾患[例えば、精神分裂症、パーキンソン病、うつ病、不安、心身症、モルヒネ依存症、痴呆(例えば、アルツハイマー病など)など]、消化器疾患[例えば、過敏性腸疾患、潰瘍性大腸炎、クローン病、ウレアーゼ陽性のラセン状グラム陰性菌(例えば、ヘリコバクター・ピロリなど)に起因する異常(例えば、胃炎、胃潰瘍など)など]、悪心、嘔吐、排尿異常(例えば、頻尿、尿失禁など)、循環器疾患(例えば、狭心症、高血圧、心不全、血栓症など)および免疫異常などの安全な予防、治療薬として有用である。とりわけ、本発明の有効成分である化合物[I]またはその薬理的に許容しうる塩は、脳内移行性が高く、且つリン脂質症誘導能がないため毒性発現に繋がる可能性が低く(安全性が高く)、副作用を殆ど示さないため、嘔吐、うつ病などの中枢神経系疾患、頻尿などの排尿異常の予防、治療薬として有用である。

[0037] 本発明の化合物またはその薬理的に許容しうる塩は、例えば、ヨーロピアン・ジャーナル・オブ・ファーマコロジー(European Journal of Pharmacology)254巻、221-227頁(1994年)記載の方法に準じて、ニューロキニン-1受容体結合作用を測定することができ、ヨーロピアン・ジャーナル・オブ・ファーマコロジー(European Journal of Pharmacology)265巻、179-183頁(1994年)記載の方法に準じて、脳内移行性を測定することができ、ブリティッシュ・ジャーナル・オブ・ファーマコロジー(British Journal of Pharmacology)119巻、931-936頁(1996年)記載の方法に準じて、嘔吐に対する作用を測定することができ、また、ジャーナル・オブ・ウロロジー(Journal of Urology)、155巻、1号、355-360頁(1996年)記載の方法に準じて、頻尿抑制作用を測定することができる。

[0038] 本発明の化合物[I]およびその薬理的に許容しうる塩は、経口的にも非経口的にも投与することができ、経口もしくは非経口投与に通常用いられる医薬担体を用いて、

dependence, dementia (for example, Alzheimer's disease, etc.), etc.], digestive organs disease [for example, irritable bowel syndrome, ulcerative colitis, Crohn's disease, disorder (for example, gastritis, gastric ulcer, etc.) related to urease-positive *Spirillum* (for example, *helicobacter pylori*, etc.), etc.], nausea, emesis, urinary disorder (for example, pollakiuria, urinary incontinence, etc.), circulatory disease (for example, angina pectoris, hypertension, cardiac failure, thrombosis, etc.) and immune disorder, etc. in mammals (for example, mouse, guinea pig, Mongolian gerbil, ferret, rat, hamster, rabbit, cat, dog, bovine, sheep, monkey, human, etc.). Particularly, since the compound [I] or a pharmaceutically acceptable salt thereof which is an active ingredient of the present invention has a high penetration to the brain and has no pospholipidosis-inducing potential, it has a small likelihood of leading to a toxicity development (has high safety) and shows almost no side effect. Therefore, it is useful as a therapeutic or prophylactic agent for central nervous system diseases such as emesis, depression and so forth, or urinary disorder such as pollakiuria, etc.

[0037]

Measurements on the compound of the present invention or a pharmaceutically acceptable salt thereof can be carried out, according to the method described in European Journal of Pharmacology, vol. 254, pp.221-227 (1994) with respect to a neurokinin-1 receptor binding action, and according to the method described in European Journal of Pharmacology, vol. 265, pp.179-183 (1994) with respect to penetration to the brain, and according to the method described in British Journal of Pharmacology, vol. 119, pp.931-936 (1996) further according to the method described in Journal of Urology, vol. 155, No. 1, pp.355-360 (1996) with regard to an inhibitory action on pollakiuria.

[0038]

The compound [I] or a pharmaceutically acceptable

salt thereof of the present invention can be administered orally or parenterally, and it can be formulated into a